GASTROENTEROLOGY

Effect of Ionizing Radiation on Gastric Secretion and Gastric Motility in Monkeys

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The prodromal syndrome of radiation sickness is characterized by nausea and vomiting but the pathophysiology and the treatment of this entity is largely unknown. We investigated this problem by determining the effects of ionizing radiation on gastric function with and without administration of the dopamine antagonist domperidone. We measured gastric electrical control activity (waves per minute), fractional emptying rate (percent per minute), acid output (microequivalents per minute), and plasma levels of immunoreactive β-endorphin. Twelve conscious, chair-adapted rhesus monkeys were studied twice before, once immediately after, and once 2 days after a single 800-cGy (800 rads) ^{60}Co total body irradiation. In addition to causing vomiting, total body irradiation transiently suppressed gastric electrical control activity, gastric emptying and gastric secretion, while increasing plasma levels of immunoreactive β-endorphin. Domperidone had no effect on vomiting or gastric function either before or after irradiation, but it significantly increased plasma immunoreactive β-endorphin.

Emesis occurs immediately after whole body irradiation and is the most obvious and the best documented prodromal symptom of radiation sickness (1, 2). Time of onset, duration, and intensity of this vomiting depend on the species (3) as well as on the type, dose rate, and total dose of irradiation (2). These symptoms are clearly different from those observed during the intestinal syndrome, which occurs 7–15 days after irradiation and is characterized by diarrhea, often accompanied by intestinal bleeding (4).

We recently studied emesis produced in dogs by total body γ-irradiation and evaluated the concurrent effect of irradiation on gastric emptying. We also determined the efficacy of an antiemetic agent, the dopamine antagonist domperidone, on vomiting as well as its effect on gastric emptying. In this dog model, gastric emptying was suppressed during the prodromal syndrome of radiation sickness. Prevention of radiation-induced vomiting with domperidone did not improve the suppression of gastric emptying (5).

The present studies were undertaken to further examine the relation between radiation-induced vomiting and stomach function in an animal model that appears to be closer to humans in terms of brain

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The experiments reported herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animals," Institute of Animal Resources, National Research Council, DHEW Publ. No. (NIH) 78-23.

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Abbreviations used in this paper: DTPA, diethylene triamine pentaacetic acid; ECA, electrical control activity; FER, fractional emptying rate; IβEND, immunoreactive β-endorphin.

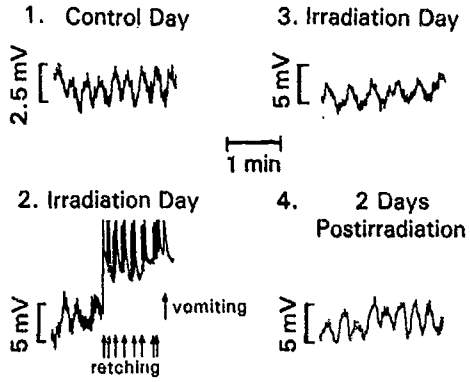

Figure 1. Examples of recording of electrical control activity obtained from abdominal bipolar electrode in 1 monkey. 1, Control day; 2, slow activity preceding six retching episodes characterized by bursts of spastic movements of the chest and abdomen (arrows) followed by a vomitus; 3, irradiation day, no vomiting but slowing of electrical activity; 4, 2 days after irradiation: no change compared with 1.

organization and gastric function. We produced vomiting in rhesus monkeys with a single dose of total body irradiation and we measured gastric acid secretion, gastric emptying of liquids, and gastric electrical control activity (ECA) before, during, and after the acute prodromal syndrome of radiation sickness. In addition, we determined plasma levels of immunoreactive β-endorphin (iβ-END) and evaluated the effect of domperidone on each of these parameters.

Materials and Methods

Twelve conscious, chair-adapted rhesus monkeys were studied on 4 separate days after an overnight fast: (a) control day after i.v. administration of placebo, (b) control day after i.v. administration of domperidone (1.0 mg/kg body wt), (c) irradiation day after administration of either placebo or domperidone, and (d) 2 days after irradiation (no drug given). This dose of domperidone was selected based on previous experiments in the dog showing that similar doses did not produce any side effect. Placebo and domperidone were given blindly and in random order on control days. Studies were performed in the morning and started 30 min after drug administration and 20 min after either sham irradiation on control days or after irradiation on irradiation day. On control days, the animals were brought to the exposure room and the doors were closed for 3 min. On irradiation day, each monkey was exposed to 800 cGy (800 rads) total body irradiation delivered at 500 cGy/min by two large, 10^5 Ci ^{60}Co irradiators placed anteriorly and posteriorly. Phantom studies demonstrated that the midline abdomen received 800 cGy and that the head received 600 cGy.

Each monkey was visually monitored for 3 h on control days and 6 h on irradiation days. Bipolar electrical potentials were recorded from two abdominal disposable skin electrodes on a multichannel recorder (Beckman R612, Beckman Instruments, Schiller Park, Ill.). Abdominal bipolar recordings displayed periodic waves in the 3-min range that have been shown to correlate with gastric ECA when gastric serosal electrodes were used in conjunction with skin electrodes (6,7). Each fasting and postload tracing was examined blindly by one of us (E. D. D.). First, the total duration during which gastric waves could be counted was determined by visual inspection (e.g., Figure 1, panels 1, 3, and 4). Of the 96 tracings obtained (12 monkeys studied on 4 separate days during fasting and after the load), 77 (80%) could be completely analyzed. Within each tracing, artifacts due to intragastric mixing or movements of the animals (e.g., retching and vomiting: Figure 1, panel 2) made the recording inadequate during ~10% of the time. Mean fasting and postload frequencies obtained in each animal on each study day were used to compute the grand mean (±SE) for each type of study in each group of animals.

Vomiting was defined as a succession of strong and brief contractions of thoracic and abdominal muscles leading to the expulsion of gastric contents through the mouth; retching was defined as a nonproductive vomiting (8). During both events, recordings displayed a succession of brief bursts of high potential spikes (Figure 1) that were clearly different from the movement artifacts that were sometimes superimposed.

A previously described and validated marker dilution technique (9,10) was used concurrently to determine gastric secretion and gastric emptying during a 40-min fasting period and for 60 min after the injection of an 80-ml water load (postload period). In the present studies, this technique was slightly modified in that ^{99m}Tc-DTPA (diethylene triamine pentaacetic acid) was used instead of phenol red as the marker. This intubation method requires only the sequential sampling of the gastric contents and permits concurrent measurement of intragastric volume, gastric emptying, and gastric secretion. A 12F double-lumen nasogastric tube was placed in the stomach and its position was verified by the water recovery test (11). Starting 45 min later, samples of the mixed gastric contents were aspirated just before and immediately after intragastric administration of 5–20 ml of a ^{99m}Tc-DTPA test solution (30 μCi/100 ml H_2O; pH 7.4; 37°C) and were centrifuged. The clear supernatant of each sample was assayed for ^{99m}Tc-DTPA concentrations using an Ultrogamma autogamma counter (LKB Instruments, Turku, Finland) and for titratable acidity using electrometric titration to pH 7.4 (Radiometer, Copenhagen, Denmark). These determinations were repeated every 10 min during the basal period and after intragastric instillation of an 80-ml water load containing ^{99m}Tc-DTPA (3 μCi/100 ml; pH 7.4; 37°C).

Intragastric volumes of fluid (V_1, V_2, . . .) and amounts of ^{99m}Tc-DTPA (Tc_1, Tc_2, . . .) were determined at the time of each sampling using the dilution principle (9,10,12,13). Fractional emptying rate (g) was then determined for each 10-min interval (t) between two dilutions, assuming that emptying was a first-order process (exponential) during a given 10-min interval and using the following equation:

$$g = -[\log_e (Tc_2/Tc_1)]/t.$$

Because g is allowed to vary from interval to interval, no general assumption has to be made regarding emptying

Table 1. Effect of Domperidone and Irradiation on Gastric Electrical Activity in Cycles per Minute (Mean ± SE)

	Control day		Irradiation day		
	Placebo	Domperidone	Placebo	Domperidone	2 days after irradiation
Fasting period	3.31 ± 0.10 (n = 12)	3.37 ± 0.12 (n = 9)	2.86 ± 0.19[a] (n = 5)	2.66 ± 0.18[a] (n = 5)	3.11 ± 0.09 (n = 11)
Postload period	3.19 ± 0.09 (n = 11)	3.15 ± 0.11 (n = 7)	2.60 ± 0.18[a] (n = 3)	2.5 ± 10.17[a] (n = 4)	3.03 ± 0.11 (n = 9)

[a] $p < 0.05$ compared with corresponding value on control day.

over the total duration of the experiment. Net fluid output (R_V) in milliliters per minute was then determined for the corresponding interval, assuming that it remained constant over the given interval and using the following equation:

$$R_V = [V_2 - V_1 \times \exp(-gt)] \times g/[1 - \exp(-gt)].$$

Intragastric volumes of fluid and masses of ^{99m}Tc-DTPA were then recalculated, taking into account these first estimates of fractional emptying and fluid output, which were in turn recalculated. This iterative process was repeated until the improvement of the solution became <1% per iteration. Having previously determined intragastric concentrations of acid (A_1, A_2, . . .), we then calculated net acid output (R_A) using the following equation:

$$R_A = [V_2 \times A_2 - V_1 \times A_1 \times \exp(-gt)] \times g/[1 - \exp(-gt)].$$

These calculations were performed using a locally developed program and a PDP-10 computer (Division of Computer Research and Technology, National Institutes of Health, Bethesda, Md.). The assumptions involved have been described and discussed elsewhere (9,10) and are based on the original contributions by Hildes and Dunlop (12) and by George (13). In contrast to their method, however, the present technique allows correction for emptying and secretion occurring during the 1-min dye dilution interval and can be applied during fasting. On irradiation day, intervals with occurrence of vomiting were not taken into account for calculation of g, R_V, or R_A.

Plasma concentrations of iβ-END were determined at the start and at the end (i.e., 2 h after sham irradiation or true irradiation) of each study using a previously described radioimmunoassay (14). Briefly, the antibody used (C-55) recognizes the region of β-END$_{1-31}$ corresponding to amino acids 17 through 26 and, therefore, detects all β-END peptides, as well as β-lipotropin, on an equimolar basis. Addition of increasing amounts of dog plasma in the assay resulted in measureable amounts of iβ-END which paralleled β-END$_{1-31}$ standard (Peninsula Labs, Inc., San Carlos, Calif.).

The statistical significance of differences observed for each measurement of gastric function [e.g., fractional emptying rate (FER), acid output] was evaluated using a three-factor (treatment, time, and monkey) analysis of variance with repeated measures on the last two factors (9,10), the program LDU-040 (K.L. Dorn), and an IBM 370 computer (Division of Computer Research and Technology, National Institutes of Health, Bethesda, Md.).

Results

No vomiting or retching was observed on control days, i.e., after sham irradiation. On irradiation day, episodes of retching or vomiting, or both, were observed and recorded (Figure 1) in 5 of 6 monkeys in the placebo group and in all the monkeys in the domperidone group. In both treatment groups, these episodes started 29 ± 3 min (mean ± SE) and ended 71 ± 9 min after irradiation. During fasting, 1 monkey in each group exhibited retching alone and 9 had retching associated with vomiting (4 after placebo and 5 after domperidone); 4 monkeys vomited once, 2 vomited twice, 2 vomited three times, and 1 vomited four times. After intragastric administration of the water load, retching was never observed alone and only 6 of 12 monkeys had retching and vomiting; when present, vomiting occurred only once and always in monkeys who had already vomited during fasting. By 2 days after irradiation, vomiting occurred in only 1 monkey; this was at the end of the study and after most of the stomach contents had been aspirated.

Fasting gastric ECA is depicted in Figure 1; ECA was 3.31 ± 0.10 per minute on control days after the placebo and was not significantly altered by domperidone (Table 1). Electrical control activity was significantly decreased after irradiation, and returned to control level 2 days after irradiation (Figure 1 and Table 1). Electrical control activity tended to be lower after the water load but the difference was not statistically significant.

Values for the FER of liquids are shown in Table 2 and in Figure 2. On control days, the FER was stable during the fasting period but more than doubled after the water load compared with fasting; this response was not significantly affected by domperidone treatment. On irradiation day, fasting FER was suppressed as soon as the study started (20 ± 2 min after exposure) and was not significantly stimulated by either the water load or domperidone. As a result, there was virtually no emptying of the water load on irradiation day in the absence of vomiting (Figure 3). A significant ($p < 0.05$) correlation ($r = 0.60$) was

Table 2. Effect of Domperidone and Irradiation on Fractional Emptying Rate, Acid Output, and Fluid Output

	Control day		Irradiation day		
	Placebo	Domperidone	Placebo	Domperidone	2 days after irradiation
FER (% min)					
Fasting (1)	4.1 ± 1.3	3.0 ± 1.2	0.4 ± 0.3[a]	0.3 ± 0.3[a]	3.4 ± 1.5
Fasting (2)	5.5 ± 1.2	3.9 ± 1.3	0.3 ± 0.2[a]	0.6 ± 0.3[a]	3.3 ± 1.2
Postload	11.8 ± 1.8	11.3 ± 1.3	0.8 ± 0.2[a]	1.3 ± 0.4[a]	12.9 ± 2.2
AO (μEq/min)					
Fasting (1)	8.5 ± 3.0	8.8 ± 3.3	5.4 ± 2.2	3.2 ± 1.0	15.2 ± 6.5
Fasting (2)	9.7 ± 3.8	8.1 ± 4.5	0.0 ± 0.0[a]	0.0 ± 0.0[a]	14.6 ± 5.0
Postload	24.4 ± 7.0	21.1 ± 8.4	1.6 ± 1.6[a]	0.0 ± 0.0[a]	27.8 ± 8.1
FO (ml/min)					
Fasting (1)	0.21 ± 0.06	0.16 ± 0.04	0.40 ± 0.12	0.30 ± 0.06	0.24 ± 0.06
Fasting (2)	0.20 ± 0.04	0.14 ± 0.03	0.23 ± 0.06	0.27 ± 0.06	0.24 ± 0.06
Postload	0.30 ± 0.04	0.29 ± 0.04	0.12 ± 0.01	0.13 ± 0.02	0.23 ± 0.05

AO, acid output; FER, fractional emptying rate; FO, fluid output. Fasting (1) corresponds to the period 0–20 min after the start of the study; on the day of irradiation, this period was 20–40 min after exposure. Fasting (2) corresponds to the period 20–40 min after the start of the study; on the day of irradiation this period was 40–60 min after exposure. Values are mean ± SE. [a] $p < 0.05$ compared with corresponding value on control day.

found between gastric ECA and mean postload FER of the stomach, the best fit being obtained with a power curve ($ECA = 3.0 \times FER^{0.021}$).

Acid output was significantly stimulated after the load compared with fasting on control days (Figure 4); domperidone did not significantly modify either fasting or postload acid output. After irradiation, acid output was suppressed in all the monkeys who had secreted on control day; the suppression started 39 ± 4 min after irradiation, persisted after load stimulation, and was not affected by domperidone (Table 2). Interestingly, acid output was not abolished in the only monkey who did not retch or vomit after irradiation.

Fluid output was significantly stimulated after the load compared with fasting on control days. After irradiation, fasting fluid output tended to be increased compared with control days, but the difference was statistically significant only in the domperidone group. After the load, fluid output was significantly suppressed in all monkeys (Table 2).

As domperidone had no significant effect on emptying, acid output, or fluid output, either in the control state or after irradiation (Table 2), values were averaged for all 12 monkeys and are depicted in Figures 2–4. Two days after irradiation, all gastric parameters had returned to control day levels, even in the monkey who had vomited on that day.

As shown in Table 3, plasma levels of iβ-END were elevated markedly by domperidone and by irradiation with placebo; the effects of radiation and the drug were additive. Two days after irradiation, plasma concentrations of iβ-END returned to basal values. Plasma levels of iβ-END were significantly ($p < 0.05$) and inversely correlated with all gastric parameters (FER: $r = 0.63$; ECA: $r = 0.61$; acid output: $r = 0.71$).

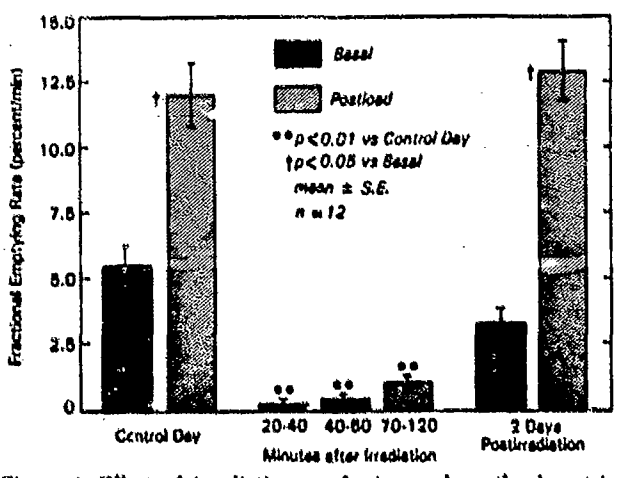

Figure 2. Effect of irradiation on fasting and postload gastric fractional emptying rate. Values are mean ± SE.

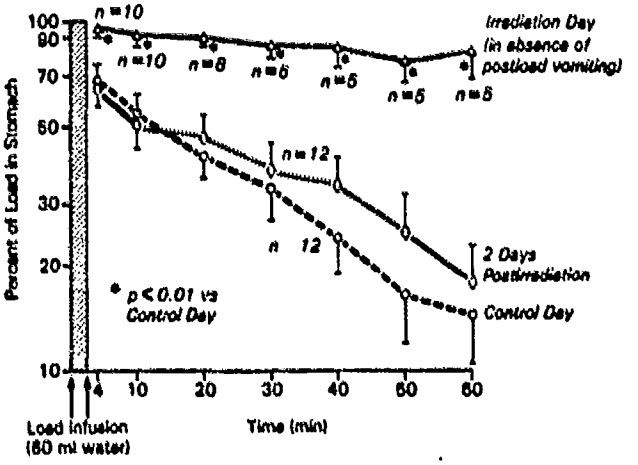

Figure 3. Effect of irradiation on the percentage of the load remaining in the stomach over time. Values are mean ± SE.

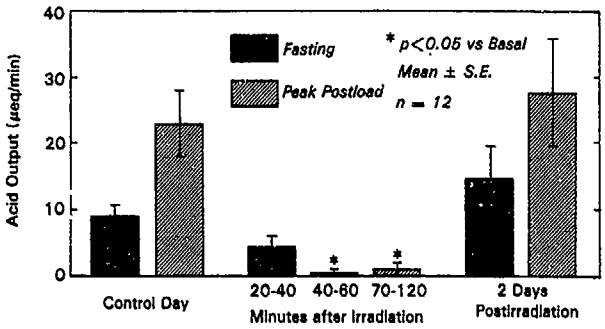

Figure 4. Effect of irradiation on basal and load-stimulated acid output. Values are mean ± SE.

Discussion

In the present studies, we report the precise and objective measurements of the immediate occurrence of retching and vomiting in rhesus monkeys exposed to total body irradiation, as well as the relation between these events, gastric function, and pituitary iβ-END secretion.

The visual distinction between retching and vomiting may be difficult in fasting monkeys, although it is easy in the presence of a large vomitus of food. Animals can either store a small vomitus into their cheek pouches and then swallow it, or they can emit some foamy saliva after a nonproductive retching. In the present studies, recording of skin potential helped in differentiating between these two types of events, demonstrating retching and vomiting in 9 of the 12 monkeys and retching alone in only 2 monkeys. This dose of 800 cGy has been selected because it is twice the ED_{50} for vomiting as previously determined by others for monkeys (1,8). Retching and vomiting started after a delay of ~30 min and disappeared after 70 min, which agrees with the observations of Middleton and Young (1) for similar doses of exposure, but markedly differ from a delay of almost an hour with doses between 400 and 550 cGy (1) and a delay of <5 min after a dose of 1200 cGy (8). Thus, the interval between irradiation and vomiting appears to be inversely proportional to the dose received.

The incidence of vomiting after irradiation appears to increase if monkeys are fed solid food 1–2 h before irradiation (8). In our study, however, a 16-h fast before irradiation does not appear to have reduced the incidence of this "radiomesis"; moreover, intragastric administration of a water load after irradiation is associated with only 6 vomiting episodes versus 18 during fasting, suggesting that the incidence of radiomesis is actually decreased by gastric distention with noncaloric liquids when irradiation is delivered at a high dose rate (500 cGy/min).

Gastric ECA may be recorded via skin electrodes as first described in 1922 (quoted in Reference 15). The frequency of this cutaneous electrogastrogram is correlated with the slow-wave frequency recorded from gastric serosal electrodes (6,7,16–18). In the present studies, the frequency of ECA was significantly decreased on the day of irradiation and had returned to basal values 2 days later; this observation has been confirmed by preliminary results obtained in monkeys with implanted gastric serosal electrodes (7). The radiation-induced decrease of ECA frequency accompanies a concurrent decrease of gastric FER both during fasting and after the load. This latter finding is similar to that observed in dogs (5,19) and in rats (20).

Our observations demonstrate that ionizing radiation has a different effect on gastric acid output and on nonparietal secretions. Immediately after irradiation, acid output is suppressed both during fasting and after a water load (Table 2 and Figure 4). This suppression of acid could be due to ultrastructural changes of parietal cells similar to those observed in the mouse within 30 min of exposure (21), but it is clearly different from the hypochlorhydria due to gastric atrophy that appears several weeks after irradiation (22–24). In contrast, fluid output is suppressed only after the water load, whereas it remains unchanged or even tends to increase during fasting (Table 2). Thus, fasting nonparietal fluid secretions appear to be increased immediately after irradiation, thereby masking the concurrent suppression of the parietal component of fluid output. As nonparietal secretions are not stimulated after a water load (9), no change of fluid output is expected during the postload period if acid output is suppressed. In fact, the significant decrease of fluid output after the water load indicates that the effect of irradiation on nonparietal secretions is biphasic, consisting of an initial stimulation followed in 40 min by an inhibition of fluid output. Two days later, however, both parietal and nonparietal secretions have returned to basal values.

The relation between radiation-induced emesis and gastric inhibition is unclear. As acid suppression starts at about the same time as vomiting and persists after its disappearance, these two symptoms may be closely related; this possibility is also sup-

Table 3. *Effect of Irradiation on Plasma Immunoreactive β-Endorphin in Picograms per Milliliter (Mean ± SE)*

Control day		125 min after irradiation		2 days after irradiation
Placebo	Domperidone	Placebo	Domperidone	
229 ± 48	881 ± 88[a]	1447 ± 228[b]	3389 ± 702[a,b]	159 ± 43

[a] $p < 0.05$ compared with placebo. [b] $p < 0.01$ compared with control day.

ported by our anecdotal finding that acid output was unchanged after irradiation in the only monkey that did not retch or vomit. In contrast, radiation-induced suppression of gastric emptying and of ECA is observed even in the 2 monkeys that did not vomit; furthermore, in the animals that did vomit, gastric emptying suppression starts before, and persists after disappearance of, emesis. Thus, radiation-induced slowing of gastric emptying may appear independently from vomiting.

The mechanism of radiation-induced emesis and gastric inhibition is probably multifactorial. The central nervous system appears to play a pivotal role in these symptoms, as suggested by the rise of plasma iβ-END observed after irradiation. This rise is similar to that observed after exposure to physical stress (25,26) and could be responsible for the observed vomiting and gastric inhibition (27,28). It is probably due to the fact that irradiation activates the peripheral end of afferent nerves or, alternatively, causes the release of humoral or toxic substances. A direct effect of irradiation on the brain appears excluded by the observation that shielding of the chemoreceptor trigger zone does not prevent radiation-induced vomiting (15).

Our observation that, in the monkey, domperidone does not prevent vomiting induced by 800-cGy ^{60}Co total body irradiation, whereas it is effective in the dog (5), could be related to the two major relevant differences that are known to exist between these two animal models: the ED_{50} for radiation-induced vomiting is lower in the dog than in the monkey (3) and, in addition, the dopamine receptor agonist apomorphine causes vomiting in dogs but not in monkeys (29). Thus, the sensitivity of dopamine receptors to their agonists and antagonists could be lesser in monkeys than in dogs. Alternatively, the blood-brain barrier surrounding the vomiting center and the chemoreceptor trigger zone may be considerably more permeable to domperidone and apomorphine in the dog as compared with the monkey. The ability of domperidone to significantly increase circulating levels of iβ-END without altering vomiting or gastric function indicates that changes in blood-borne iβ-END do not solely account for the effects of radiation on gastric function. These findings, however, are consistent with the demonstration that dopaminergic receptor blockade results in the release of pituitary iβ-END in both dogs and rats (30,31); taken together, they suggest that dopaminergic inhibition of pituitary iβ-END release is a common feature among mammals.

In conclusion, radiation-induced emesis is accompanied by a suppression of gastric emptying and acid secretion. The concurrent slowing of gastric ECA suggests that an alteration of the motility of the stomach is responsible for the suppression of gastric emptying. The time of onset of each symptom after irradiation and the transiency of the acute prodromal syndrome to radiation sickness suggest the involvement of neural or neurohormonal mechanisms, or both, or a receptor inactivation (32). The release of pituitary iβ-END demonstrated by the present studies could mediate these effects and, in addition, clearly indicates an alteration of brain function. Thus, the central nervous system appears to play a pivotal role in the digestive symptoms that immediately follow total body irradiation.

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